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(54) Title: METHODS FOR TREATING NEUROPSYCHIATRIC DISORDERS

(57) Abstract

The invention provides methods for treating neuropsychiatric disorders such as schizophrenia, Alzheimer's Disease, autism, depression, benign forgetfulness, childhood learning disorders, close head injury, and attention deficit disorder. The methods entail administering to a patient diagnosed as having a neuropsychiatric disorder a pharmaceutical composition containing (i) a therapeutically effective amount of D–alanine (or a modified form thereof), provided that the composition is substantially free of D–cycloserine, and/or (ii) D–serine (or a modified form thereof), and/or (iii) 105 to 500 mg of D–cycloserine (or a modified form thereof), and/or (iv) N–methylglycine (or a modified form thereof).

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METHODS FOR TREATING NEUROPSYCHIATRIC DISORDERS

Background of the Invention

Schizophrenia, Alzheimer's Disease, autism, depression, benign forgetfulness, childhood learning disorders, close head injury, and attention deficit disorder are examples of neuropsychiatric disorders. Autism, for example, is a developmental mental disorder characterized by autistic behavior, social failure, and language delay. Alzheimer's Disease is a form of dementia that typically involves progressive mental deterioration, manifested by memory loss, confusion, and disorientation. Alzheimer's Disease typically is treated by acetylcholine esterase inhibitors such as tacrine hydrochloride or donepezil. Attention Deficit Disorder is a disorder that is most prevalent in children and is associated with increased motor activity and a decreased attention span. Attention Deficit Disorder commonly is treated by administration of psychostimulants such as Ritalin or Dexedrin. Depression is a clinical syndrome that includes a persistent sad mood or loss of interest in activities, which persists for at least two weeks in the absence of treatment. Conventional therapeutics include serotonin uptake inhibitors (e.g., PROZAC™), monoamine oxidase inhibitors, and tricyclic antidepressants.

The term schizophrenia represents a group of neuropsychiatric disorders characterized by dysfunctions of the thinking process, such as delusions, hallucinations, and extensive withdrawal of the patient's interests from other people. Approximately one percent of the worldwide population is afflicted with schizophrenia, and this disorder is accompanied by high morbidity and mortality rates.

Conventional antipsychotic drugs, which act on the dopamine D_2 receptor, can be used to treat the positive symptoms of schizophrenia, such as delusion and hallucination. In general, conventional antipsychotic drugs and the new atypical antipsychotic drugs, which act on the dopamine D_2 and $5HT_2$ serotonin receptor, are limited in their ability to treat cognitive deficits and negative symptoms such as affect blunting (i.e., lack of facial expressions), anergia, and social withdrawal.

Summary of the Invention

The invention derives from the discovery that neuropsychiatric disorders characterized by a deficit in neurotransmission via the NMDA receptor can be alleviated by a compound that acts as an agonist of the glycine site on the NMDA receptor or an inhibitor of glycine uptake. The compound is either a partial agonist such as D-cycloserine, which can be used at a dosage of 105-500 mg, or a full agonist (e.g., D-serine or D-alanine) that is selective for the NMDA receptor (compared to the inhibitory glycine receptor and other receptors), or a glycine uptake inhibitor (e.g., N-methylglycine). The invention therefore provides new methods for treating neuropsychiatric disorders in patients (i.e., humans). Examples of disorders that can be treated by the methods of the invention include schizophrenia, Alzheimer's Disease, autism, depression, benign forgetfulness, childhood learning disorders, close head injury, and attention deficit disorder. The methods entail administering to a patient diagnosed as suffering from such a neuropsychiatric disorder a pharmaceutical composition that contains a therapeutically effective amount of an agonist of the glycine site of the NMDA receptor or a glycine uptake inhibitor, which agonist is relatively selective for (a) the glycine site of the NMDA

receptor, compared with (b) the inhibitory glycine receptor and other receptors. The pharmaceutical composition may include, for example, (i) a therapeutically effective amount of D-alanine (wherein the pharmaceutical composition is substantially free of D-cycloserine) and/or (ii) a therapeutically effective amount of D-serine, and/or (iii) D-cycloserine in an amount of 105-500 mg, and/or (iv) a therapeutically effective amount of N-methylglycine.

In variations of the methods described herein, D-serine, D-alanine, D-cycloserine, and/or N-methylglycine can be substituted with a salt, ester, or alkylated form of the amino acid, or a precursor of the amino acid that is converted (e.g., metabolized) into the amino acid *in vivo* (e.g., D-phosphoserine, L-phosphoserine, or L-phosphoserine, N,N,N-trimethylglycine (betaine), or N,N-dimethylglycine).

Typically, a dosage of 100 μg to 100 g (e.g., 1 mg to 100 g; 1 mg to 100 mg; 10 mg to 100 g; 10 mg to 10 g; or 10 to 500 mg) is suitable for D-alanine, D-serine, and N-methylglycine. D-cycloserine is administered at a dosage of 105 to 500 mg. When the patient is treated with both D-serine and D-alanine, D-serine and D-alanine can be administered to the patient simultaneously or sequentially, e.g., by formulating the D-serine and D-alanine as a single pharmaceutical composition or as two or more pharmaceutical compositions. Likewise, the patient can be treated with both D-serine and D-cycloserine, or D-serine and N-methylglycine, or D-alanine and N-methylglycine, or D-cycloserine and N-methylglycine simultaneously or sequentially. In one, but not the only, suitable method of treatment, the pharmaceutical composition is administered to the patient at least once daily for at least one week. If desired, the pharmaceutical composition can be administered to the

patient in more than one dose per day (e.g., 2, 3, or 4 doses). Generally, the patient is treated for at least one week; typically, the patient is treated for at least several weeks (e.g., at least 4, 6, or 8 weeks) or months (e.g., at least 4, 8, or 12 months). If necessary, the treatment can continue indefinitely to keep the patient's symptoms under control throughout his or her life.

If desired, a pharmaceutical composition containing D-alanine (substantially free of D-cycloserine), D-serine, D-cycloserine and/or N-methylglycine (or a modified version thereof, as described herein) can be administered to a patient suffering from schizophrenia along with, or in sequence with, an art-known drug for treating schizophrenia (e.g., olanzapine, clozapine, haloperidol, and the like). Similarly, D-alanine (typically substantially free of D-cycloserine), D-serine, D-cycloserine and/or N-methylglycine (or a modified version thereof, as described herein) can be used in combination with, or in sequence with, other art-known antipsychotics (e.g., "typical," "atypical," and depot antipsychotics for treating schizophrenia and other psychotic conditions), antidepressants (for treating depression), psychostimulants (for treating attention deficit disorder, depression, or learning disorders), or Alzheimer's disease therapeutics (for treating Alzheimer's disease). Such pharmaceutical compositions are included within the invention. In general, the antipsychotic, antidepressant, psychostimulant, or Alzheimer's disease therapeutic typically is administered at a dosage of 0.25-5000 mg/d (e.g., 5-1000 mg/d)). "Typical" antipsychotics are conventional antipsychotics such as phenothiazine, butryophenones, thioxantheses, dibenzoxazepines, dihydroindolones, and diphenylbutylpiperidines. "Atypical" antipsychotics are

a new generation of antipsychotics which generally act on the dopamine D_2 and $5HT_2$ serotonin receptor and have high levels of efficacy and a benign extrapyramidal symptom side effect profile. Examples of typical antipsychotics (and examples of suitable daily (d) dosages) include Chlorpromazine (5-2000 mg/d, e.g., 30-800 mg/d), Thioridazine (5-2000 mg/d, e.g., 20-800 mg/d), Mesoridazine (1-1000 mg/d, e.g., 30-400 mg/d), Fluphenazine (0.5-200 mg/d, e.g., 1-40 mg/d), Perphenazine (0.5-300 mg/d, e.g., 10-65 mg/d), Trifluoperazine (0.5-200 mg/d, e.g., 2-40 mg/d), Thiothixene (1-200 mg/d, e.g., 6-60 mg/d), Haloperidol (0.25-500 mg/d, e.g., 1-100 mg/d), Loxapine (1-1000 mg/d e.g., 20-250 mg/d), Molindone (1-1000 mg/d, e.g., 15-225 mg/d), Acetophenazine (10-2000 mg/d, e.g., 30-500 mg/d), Chlorprothixene (5-2000 mg/d, e.g., 30-500 mg/d), Droperidol (0.25-500 mg/d, e.g., 1-100 mg/d), Pimozide (0.25-500 mg/d, e.g., 1-100 mg/d). Examples of atypical antipsychotics (and examples of suitable daily dosages) include Clozapine (5-2000 mg/d, e.g., 12-900 mg/d), Risperidone (0.25-500 mg/d, e.g., 2-16 mg/d), Olanzapine (1-100 mg/d, e.g., 5-10 mg/d), and Quetiapine (1-2000 mg/d, e.g., 50-750 mg/d). Depot antipsychotics also can be used, e.g., Haloperidol decanoate (10-1000 mg/month, e.g., 100-450 mg/month), Fluphenazine decanoate (5-1000 mg/month, e.g., 25-150 mg/month), and Fluphenazine enanthate (5-1000 mg/month, e.g., 25-200 mg/month). Additional antipsychotics include Butaperazine (0.5-500 mg/d, e.g., 1-200 mg/d), Carphenazine, (0.5-3000 mg/d, e.g., 1-1000 mg/d), Remoxipride (0.5-5000 mg/d, e.g., 1-2000 mg/d), Piperacetazine (0.5-500 mg/d, e.g., 1-2000 mg/d), Sulpiride (0.5-5000 mg/d, e.g., 1-2000 mg/d), and Ziprasidone (0.5-500 mg/d, e.g., 1-200 mg/d). Examples of antidepressants that can be used include Amitriptyline

(5-1000 mg/d, e.g., 50-300 mg/d), Amoxapine (5-1000 mg/d, e.g., 50-600 mg/d), Bupropion (5-1000 mg/d, e.g., 200-450 mg/d), Bupropion SR (5-1000 mg/d, e.g., 150-400 mg/d), Clomipramine (5-1000 mg/d, e.g., 25-250 mg/d), Desipramine (5-1000 mg/d, e.g., 100-300 mg/d), Doxepin (5-1000 mg/d, e.g., 75-300 mg/d), Fluoxetine (1-200 mg/d, e.g., 20-80 mg/d), Fluvoxamine (5-1000 mg/d, e.g., 50-300 mg/d), Imipramine (5-1000 mg/d, e.g., 75-300 mg/d), Maprotiline (5-1000, e.g., 75-225 mg/d), Mirtazapine (1-200 mg/d, e.g., 15-45 mg/d), Nefazodone (5-1000 mg/d, e.g., 200-600 mg/d), Nortriptyline (5-1000 mg/d, e.g., 75-150 mg/d), Paroxetine (1-200 mg/d, e.g., 10-60 mg/d), Phenelzine (1-500 mg/d, e.g., 5-90 mg/d), Protriptyline (1-200 mg/d, e.g., 15-60 mg/d), Sertraline (5-1000 mg/d, e.g., 50-200 mg/d), Tranylcypromine (1-200 mg/d, e.g., 30-60 mg/d), Trazodone (5-1000 mg/d, e.g., 150-600 mg/d), Trimipramine (5-1000 mg/d, e.g., 5-300 mg/d), Venlafaxine (5-1000 mg/d, e.g., 75-375 mg/d), and Venlafaxine XR (5-1000 mg/d, e.g, 75-225 mg/d). Psychostimulants that are particularly useful for treating attention deficit disorder include Dextroamphetamine (0.5-200 mg/d, e.g., 5-40 mg/d), Methamphetamine (0.5-200 mg/d, e.g., 5-25 mg/d), Methylphenidate (0.5-200 mg/d, e.g., 10-40 mg/d), and Pemoline (5-500 mg/d, e.g., 37.5-112.5 mg/d). Examples of Alzheimer's disease therapeutics that can be used in the invention include Donepezil (0.5-200 mg/d, e.g., 1-100 mg/d) and Tacrine (0.5-1000 mg/d, e.g., 10-500 mg/d). Thus, the invention also provides pharmaceutical compositions that contain D-alanine (typically substantially free of D-cycloserine), D-serine, D-cycloserine and/or N-methylglycine (or a modified version thereof, as described herein) along with an antipsychotic, antidepressant, psychostimulant, or Alzheimer's disease therapeutic.

If desired, one can measure negative and/or positive and/or cognitive symptom(s) of schizophrenia before and after treatment of the patient. A reduction in such a symptom indicates that the patient's condition has improved. Improvement in the symptoms of schizophrenia can be assessed using the Scales for the Assessment of Negative Symptoms (SANS) or Positive and Negative Syndrome Scale (PANSS) (see, e.g., Andreasen, 1983, *Scales for the Assessment of Negative Symptoms (SANS)*, Iowa City, Iowa and Kay et al., 1987, Schizophrenia Bulletin 13:261-276). Likewise, one can measure improvement of other neuropsychiatric disorders in patients who have been treated by the methods of the invention.

As used herein, the term "neuropsychiatric disorder" refers to a disease having a pathophysiological component of attenuated NMDA receptor-mediated neurotransmission. Examples of such disorders include schizophrenia, Alzheimer's disease, autism, depression, benign forgetfulness, childhood learning disorders, close head injury, and attention deficit disorder.

As used herein, the term "schizophrenia" refers to a psychiatric disorder that includes at least two of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms. Patients can be diagnosed as schizophrenic using the DSM-IV criteria (APA, 1994, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition), Washington, DC).

The term "Alzheimer's Disease" refers to a progressive mental deterioration manifested by memory loss, confusion and disorientation beginning in late middle life and typically resulting in death in five to ten years. Pathologically, Alzheimer's Disease can be characterized by thickening, conglutination, and

distortion of the intracellular neurofibrils, neurofibrillary tangles and senile plaques composed of granular or filamentous argentophilic masses with an amyloid core. Methods for diagnosing Alzheimer's Disease are known in the art. For example, the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease-and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria can be used to diagnose Alzheimer's Disease (McKhann et al., 1984, Neurology 34:939-944). The patient's cognitive function can be assessed by the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog; Rosen et al., 1984, Am. J. Psychiatry 141:1356-1364).

As used herein, the term "autism" refers to a state of mental introversion characterized by morbid self-absorption, social failure, language delay, and stereotyped behavior. Patients can be diagnosed as suffering from autism by using the DSM-IV criteria.

As used herein, the term "depression" refers to a clinical syndrome that includes a persistent sad mood or loss of interest in activities, which lasts for at least two weeks in the absence of treatment. The DSM-IV criteria can be used to diagnose patients as suffering from depression.

The term "benign forgetfulness," as used herein, refers to a mild tendency to be unable to retrieve or recall information that was once registered, learned, and stored in memory (e.g., an inability to remember where one placed one's keys or parked one's car). Benign forgetfulness typically affects individuals after 40 years of age and can be recognized by standard assessment instruments such as the Wechsler Memory Scale (Russell, 1975, J. Consult Clin. Psychol. 43:800-809).

As used herein, the term "childhood learning disorders" refers to an impaired ability to learn, as

experienced by certain children. Such learning disorders can be diagnosed by using the DSM-IV criteria.

The term "close head injury," as used herein, refers to a clinical condition after head injury or trauma which condition can be characterized by cognitive and memory impairment. Such a condition can be diagnosed as "amnestic disorder due to a general medical condition" according to DSM-IV.

The term "attention deficit disorder," as used herein, refers to a disorder that is most commonly exhibited by children and which can be characterized by increased motor activity and a decreased attention span. The DSM-IV criteria can be used to diagnose attention deficit disorder.

The terms "D-serine" and "D-alanine" refer to the D isomers of the amino acids serine and alanine, respectively. As D isomers, rather than L isomers, these amino acids are not naturally found in proteins.

"Negative" symptoms of schizophrenia include affect blunting, anergia, alogia and social withdrawal, which can be measured using SANS (the Scales for the Assessment of Negative Symptoms; see Andreasen, 1983, *Scales for the Assessment of Negative Symptoms (SANS)*, Iowa City, Iowa).

"Positive" symptoms of schizophrenia include delusion and hallucination, which can be measured using PANSS (the Positive and Negative Syndrome Scale; see Kay et al., 1987, Schizophrenia Bulletin 13:261-276).

"Cognitive" symptoms of schizophrenia include impairment in obtaining, organizing, and using intellectual knowledge which can be measured by the Positive and Negative Syndrome Scale-cognitive subscale (PANSS-cognitive subscale) (Lindenmayer et al., 1994, J. Nerv. Ment. Dis. 182:631-638) or with cognitive tasks such as the Wisconsin Card Sorting Test.

A "full" agonist of the NMDA receptor is a compound that produces a maximal response at full receptor occupancy.

A "partial" agonist of the NMDA receptor is a compound that produces a lower maximal response at full receptor occupancy than do full agonists.

A "glycine uptake inhibitor of the NMDA receptor" is a compound that inhibits the re-uptake of glycine and increases the availability of glycine for the NMDA receptor (e.g., N-methylglycine).

The invention offers several advantages over many art-known methods for treating neuropsychiatric disorders. For example, unlike many conventional antipsychotic therapeutics, D-serine, D-alanine, and N-methylglycine can produce a desirable reduction in the positive, negative, and cognitive symptoms of schizophrenia. As shown by the examples set forth below, clinically significant improvement can be achieved even with patients who are poorly responsive to treatment by conventional antipsychotics. In addition, no significant side effects were detected after treatment of schizophrenia patients with D-serine, D-alanine, or N-methylglycine. In contrast, conventional antipsychotics typically lead to tardive dyskinesia (irreversible, involuntary movement disorder), extrapyramidal symptoms, and akathesia symptoms.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

Detailed Description

The invention provides methods for treating a patient diagnosed as suffering from a neuropsychiatric disorder having a deficit in neurotransmission via the NMDA receptor (e.g., schizophrenia, Alzheimer's Disease,

autism, depression, benign forgetfulness, childhood learning disorders, close head injury, and attention deficit disorder). As described above, a variety of methods for diagnosing these disorders are known to those of skill in the art of clinical psychiatry, and any conventional diagnostic method can be used in conjunction with the invention.

The treatment method of the invention entails administering to a patient diagnosed as having a neuropsychiatric disorder a pharmaceutical composition containing a therapeutically effective amount of (i) an agonist of the glycine site of the NMDA receptor, which agonist is relatively selective for (a) the glycine site of the NMDA receptor, compared with (b) an inhibitory glycine receptor or any other receptor, or (ii) a glycine uptake inhibitor. For example, suitable pharmaceutical compositions may include (i) D-alanine substantially free of D-cycloserine and/or (ii) D-serine and/or (iii) N-methylglycine. D-serine and D-alanine are commercially available (e.g., from Spectrum Quality Products, Inc., Gardena, CA). Where D-alanine is used, the pharmaceutical composition is "substantially free" of D-cycloserine, meaning that the composition lacks D-cycloserine, or D-cycloserine is not included at a level sufficient to have a statistically significant effect upon the efficacy of the pharmaceutical composition, as determined by any method (e.g., by comparing PANSS and/or SANS scores before and after treatment of the patient). In general, this means that D-cycloserine is absent from the pharmaceutical composition or present in an amount such that the patient receives less than 0.02 mg/day.

Treatment includes administering a therapeutically effective amount of a composition containing D-alanine (substantially free of D-cycloserine) and/or D-serine and/or N-methylglycine to a patient in need of such

treatment, thereby treating the neuropsychiatric disorder. Such compositions typically contain from about 0.1 to 90% by weight (such as 1 to 20% or 1 to 10%) of D-alanine, D-serine, or N-methylglycine in a pharmaceutically acceptable carrier. Regardless of the concentration of D-serine or D-alanine in the pharmaceutical composition, D-serine and/or D-alanine and/or N-methylglycine is administered to the patient at a dosage of 10 mg to 100 g. More typically, D-serine and/or D-alanine and/or N-methylglycine is administered at a dosage of 100 mg to 10 g. Generally, treatment continues for at least several weeks to several years or life-long as needed.

In an alternative method for treating a neuropsychiatric disorder in a patient, a pharmaceutical composition containing D-cycloserine in an amount equivalent to a dosage of 105 to 500 mg/day is administered to a patient in need of such treatment. For example, the dosage can be in an amount of 125 to 400 mg, such as 150 to 300 mg (e.g., 175 mg, 200 mg, 225 mg, or 250 mg). D-cycloserine (D-4-amino-3-isoxazolidinone) is commercially available from Eli Lilly, Inc. (Indianapolis, IN). Generally, treatment continues for at least one week and can continue for several years or life-long as needed to control the patient's symptoms.

In all of the methods of the invention, D-alanine, D-serine, and/or D-cycloserine and/or N-methylglycine can be substituted with a modified version of the amino acid, such as a salt, ester, alkylated form, or a precursor of the amino acid. For example, the amino acid can be in the form of a sodium salt, potassium salt, calcium salt, magnesium salt, zinc salt, or ammonium salt. Such salt forms of D-serine, D-alanine, N-methylglycine and D-cycloserine can be made in accordance with conventional methods (see, e.g., *Organic Chemistry*, pgs. 822-823,

Morrison and Boyd, *ed.*, Fifth Edition, Allyn and Bacon, Inc., Newton, MA). Other modified forms of D-serine, D-alanine, N-methylglycine and D-cycloserine also can be used in the methods of the invention. For example, the carboxy group of the amino acid can be converted to an ester group by reaction with an alcohol in accordance with standard esterification methods (*Id.* at 841-843). For example, alcohols having 1-20 carbon atoms can be used to produce an ester of D-serine, D-alanine, N-methylglycine or D-cycloserine for use in the invention (e.g., methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, sec-butyl-, tert-butyl-, pentyl-, isopentyl-, tert-pentyl-, hexyl-, heptyl-, octyl-, decyl-, dodecyl-, tetradecyl-, hexadecyl-, octadecyl-, and phenyl-alcohols can be used). In another variation, the amino group of the amino acid can be alkylated, using conventional methods, to produce a secondary or tertiary amino group by ammonolysis of halides or reductive amination (*Id.* at 939-948). For example, an alkyl group having 1-20 carbon atoms can be added to the amino acid to produce an alkylated amino acid (e.g., methyl-, ethyl-, propyl-, isopropyl-, butyl-, isobutyl-, sec-butyl-, tert-butyl-, pentyl-, isopentyl-, tert-pentyl-, hexyl-, heptyl-, octyl-, decyl-, dodecyl-, tetradecyl-, hexadecyl-, octadecyl- and phenyl-groups can be added to the amino acid). D-phosphoserine and L-phosphoserine are examples of precursors of D-serine, and are commercially available (e.g., from Sigma Chemical, St. Louis, MO). N,N,N-trimethylglycine (betaine) and N,N-dimethylglycine are examples of precursors of N-methylglycine.

In all of the methods of the invention, appropriate dosages of D-alanine, D-serine, D-cycloserine, or N-methylglycine (or modified versions thereof) can readily be determined by those of ordinary skill in the art of medicine by monitoring the patient

for signs of disease amelioration or inhibition, and increasing or decreasing the dosage and/or frequency of treatment as desired.

The pharmaceutical compositions can be administered to the patient by any, or a combination, of several routes, such as oral, intravenous, trans-mucosal (e.g., nasal, vaginal, etc.), pulmonary, transdermal, ocular, buccal, sublingual, intraperitoneal, intrathecal, intramuscular, or long term depot preparation. Solid compositions for oral administration can contain suitable carriers or excipients, such as corn starch, gelatin, lactose, acacia, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, calcium carbonate, sodium chloride, lipids, alginic acid, or ingredients for controlled slow release. Disintegrators that can be used include, without limitation, micro-crystalline cellulose, corn starch, sodium starch glycolate and alginic acid. Tablet binders that may be used include, without limitation, acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone), hydroxypropyl methylcellulose, sucrose, starch, and ethylcellulose.

Liquid compositions for oral administration prepared in water or other aqueous vehicles can include solutions, emulsions, syrups, and elixirs containing, together with the active compound(s), wetting agents, sweeteners, coloring agents, and flavoring agents. Various liquid and powder compositions can be prepared by conventional methods for inhalation into the lungs of the patient to be treated.

Injectable compositions may contain various carriers such as vegetable oils, dimethylacetamide, dimethylformamide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, polyols (glycerol, propylene glycol, liquid polyethylene glycol, and the

like). For intravenous injections, the compounds may be administered by the drip method, whereby a pharmaceutical composition containing the active compound(s) and a physiologically acceptable excipient is infused. Physiologically acceptable excipients may include, for example, 5% dextrose, 0.9% saline, Ringer's solution or other suitable excipients. For intramuscular preparations, a sterile composition of a suitable soluble salt form of the compound can be dissolved and administered in a pharmaceutical excipient such as Water-for-Injection, 0.9% saline, or 5% glucose solution, or depot forms of the compounds (e.g., decanoate, palmitate, undecylenic, enanthate) can be dissolved in sesame oil. Alternatively, the pharmaceutical composition can be formulated as a chewing gum, lollipop, or the like.

EXAMPLES

The following examples demonstrate that D-alanine, D-serine, and N-methylglycine each can be used to treat a neuropsychiatric disorder in patients.

Patients

This study employed 37 patients who were diagnosed as having schizophrenia. All patients fulfilled the DSM-IV diagnosis of schizophrenia (APA, 1994, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Washington, DC). All of the patients also fulfilled the criteria of primary deficit syndrome, with a SANS score of more than 40 (Kirkpatrick et al., 1989, Psychiatry Research 30:119-123; Andreasen, 1983, Scales for the Assessment of Negative Symptoms (SANS), Iowa City, Iowa). All of the patients were poorly responsive to treatment by other antipsychotic drugs, and had been kept on a stable dose of an

antipsychotic drug for at least 3 months prior to enrollment in this study.

Assessments

Several scales were used to assess the severity of the disorder in each patient. At the beginning of the study (i.e., the baseline), the PANSS, SANS, and Global Assessment Scales (CGI) were used. Each scale also was completed at the end of each 2-week period throughout the study. These assessments were performed by a psychiatrist who was blind to the treatment assignment. The Wisconsin Card Sort Test was used to provide a cognitive rating of the patients; in general, schizophrenic patients perform poorly on this test. The Wisconsin Card Sort Test was administered only at the initiation of the study and at the end of the 6-week study. To measure side effects, the Simpson-Angus Scale was used to measure extrapyramidal symptoms (EPS; Simpson et al., 1970, Acta Psychiatrica Scandinavia Suppl. 212:11-19). The Abnormal Involuntary Movement Scale (AIMS) was used to measure dyskinesia (Simpson et al., 1970, Acta Psychiatrica Scandinavia Suppl. 212:11-19). The Barnes Scale was used to measure akathesia (Barnes, 1989, Brit. J. Psychiatry 154:672-676). The side effects of D-serine, D-alanine, and N-methylglycine treatments were assessed biweekly according to the UKU side effects rating scale (*Scandinavian Society of Psychopharmacology Committee of Clinical Investigation: The UKU side effect rating scale: scale for the registration of unwanted effects of psychotropics*. Acta. Psychiatr. Scand. 1987; Suppl. 334:81-94).

Treatment and Results

Using double-blind conditions, the patients were randomly assigned to receive placebo (fruit juice), D-

serine (30 mg/kg/day), D-alanine (60-100 mg/kg/day), or N-methylglycine (30 mg/kg/day) once a day by mouth for a period of 6 weeks. As indicated by the results shown in Table 1, treatment with D-serine, D-alanine, or N-methylglycine improved the schizophrenic symptoms and cognitive deficit of the patients. More specifically, treatment with D-serine resulted in a 21% reduction of the negative symptoms (on the SANS scale), and it resulted in a 17% reduction of the positive symptoms (on the PANSS-positive subscale). Treatment with D-alanine resulted in an 11% reduction of the negative symptoms and a 12% reduction of the positive symptoms. Treatment with N-methylglycine resulted in a 20% reduction of the negative symptoms and a 15% reduction of the positive symptoms. These reductions in the negative and positive symptoms represented clinically significant improvement. Treatment with each of D-serine, D-alanine, and N-methylglycine also improved cognition, as measured using the PANSS-cognitive subscale and the Wisconsin Card Sort Test. These results indicate that D-serine, D-alanine, and N-methylglycine are effective in treating schizophrenia even in patients who are poorly responsive to treatment by conventional antipsychotic drugs.

Using the UKU scale for rating side effects, no side effects were noted after treatment with D-serine, D-alanine, or N-methylglycine. In addition, there was no newly emergent tardive dyskinesia or worsening of extrapyramidal or akathesia symptoms. Thus, D-serine, D-alanine, and N-methylglycine offer an advantage over many conventional drugs for treating schizophrenia in that they do not cause significant side effects.

TABLE 1: Effects of D-serine, D-alanine, and N-methylglycine Treatment on Schizophrenia Patients

	D-serine	D-alanine	N-methylglycine	Placebo
Clinical Symptoms				
Negative Symptoms	-21%*	-12%*	-20%*	-1%
Positive Symptoms	-17%*	-11%*	-15%*	3%
CGI	4.8->2.6*	3.9->2.8*	4.2->2.7*	4.5->4.0
Cognition				
Cognitive symptoms	-12%*	-11%*	-12%*	1%
WCST	+0.9 (category)*	+0.5*	+0.7*	-0.5
Side Effects				
EPS	1.4-->1.7	3.1-->3.1	2.1-->2.1	3.3-->3.4
AIMS	0.3-->0.3	0.5-->0.1	0.4-->0.3	0.5-->0.9
Barnes	0.4-->0.8	0.4-->0.6	0.5-->0.6	0.9-->0.9

* Clinically significant improvement

Other Embodiments

It is to be understood that, while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A method for treating a neuropsychiatric disorder characterized by attenuated NMDA neurotransmission in a patient, the method comprising administering to a patient diagnosed as suffering from the neuropsychiatric disorder a pharmaceutical composition comprising a therapeutically effective amount of an agonist of the glycine site of an NMDA receptor or a glycine uptake inhibitor, wherein:

the agonist is selected from the group consisting of D-alanine, a salt of D-alanine, an ester of D-alanine, alkylated D-alanine, a precursor of D-alanine, D-serine, a salt of D-serine, an ester of D-serine, alkylated D-serine, a precursor of D-serine, D-cycloserine, a salt of D-cycloserine, an ester of D-cycloserine, a precursor of D-cycloserine, and alkylated D-cycloserine;

the pharmaceutical composition is substantially free of D-cycloserine when the agonist is D-alanine, a salt of D-alanine, an ester of D-alanine, an alkylated D-alanine, or a precursor of D-alanine; and

when the agonist is D-cycloserine, a salt of D-cycloserine, an ester of D-cycloserine, a precursor of D-cycloserine, or alkylated D-cycloserine, the pharmaceutical composition comprises an amount of the agonist equivalent to 105-500 mg of D-cycloserine.

2. The method of claim 1, wherein the neuropsychiatric disorder is schizophrenia.

3. The method of claim 1, wherein the neuropsychiatric disorder is Alzheimer's disease.

4. The method of claim 1, wherein the neuropsychiatric disorder is autism.

5. The method of claim 1, wherein the neuropsychiatric disorder is depression.

6. The method of claim 1, wherein the neuropsychiatric disorder is benign forgetfulness.

7. The method of claim 1, wherein the neuropsychiatric disorder is a childhood learning disorder.

8. The method of claim 1, wherein the neuropsychiatric disorder is attention deficit disorder.

9. The method of claim 1, wherein the neuropsychiatric disorder is close head injury.

10. The method of claim 1, wherein the agonist is selected from the group consisting of D-alanine, a salt of D-alanine, an ester of D-alanine, alkylated D-alanine, and a precursor of D-alanine.

11. The method of claim 10, wherein the D-alanine, salt of D-alanine, ester of D-alanine, alkylated D-alanine, or precursor of D-alanine is administered at a dosage equivalent to 10 mg to 100 g of D-alanine.

12. The method of claim 10, wherein the agonist is a D-alanine salt selected from the group consisting of a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a zinc salt, and an ammonium salt of D-alanine.

13. The method of claim 10, wherein the agonist is an ester of D-alanine having an ester group with 1-20 carbon atoms.

14. The method of claim 10, wherein the agonist is an alkylated D-alanine having an alkyl group with 1-20 carbon atoms.

15. The method of claim 10, wherein the pharmaceutical composition further comprises D-serine.

16. The method of claim 1, wherein the agonist is selected from the group consisting of D-serine, a salt of D-serine, an ester of D-serine, alkylated D-serine, and a precursor of D-serine.

17. The method of claim 16, wherein the D-serine, salt of D-serine, ester of D-serine, precursor of D-serine, or alkylated D-serine is administered at a dosage equivalent to 10 mg to 100 g of D-serine.

18. The method of claim 16, wherein the agonist is a D-serine salt selected from the group consisting of a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a zinc salt, and an ammonium salt of D-serine.

19. The method of claim 16, wherein the agonist is an ester of D-serine having an ester group with 1-20 carbon atoms.

20. The method of claim 16, wherein the agonist is an alkylated D-serine having an alkyl group with 1-20 carbon atoms.

21. The method of claim 1, wherein the agonist is selected from the group consisting of D-cycloserine, a salt of D-cycloserine, an ester of D-cycloserine, a precursor of D-cycloserine, and an alkylated D-cycloserine.

22. The method of claim 21, wherein the D-cycloserine, salt of D-cycloserine, ester of D-cycloserine, alkylated D-cycloserine, or precursor of D-cycloserine is administered in a dose equivalent to 125-400 mg of D-cycloserine.

23. The method of claim 22, wherein the D-cycloserine, D-cycloserine salt, ester of D-cycloserine, alkylated D-cycloserine, or precursor of D-cycloserine is administered in a dose equivalent to 150-300 mg of D-cycloserine.

24. The method of claim 21, wherein the pharmaceutical composition comprises a salt of D-cycloserine selected from the group consisting of a sodium salt, a potassium salt, a calcium salt, a magnesium salt, a zinc salt, and an ammonium salt of D-cycloserine.

25. The method of claim 21, wherein the pharmaceutical composition comprises an ester of D-cycloserine having an ester group with 1-20 carbon atoms.

26. The method of claim 21, wherein the pharmaceutical composition comprises an alkylated D-cycloserine having an alkyl group with 1-20 carbon atoms.

27. The method of claim 21, wherein the pharmaceutical composition comprises a precursor of D-cycloserine.

28. The method of claim 1, wherein the glycine uptake inhibitor is selected from the group consisting of N-methylglycine, a salt of N-methylglycine, an ester of N-methylglycine, and a precursor of N-methylglycine.

29. The method of claim 28, wherein the N-methylglycine, salt of N-methylglycine, ester of N-methylglycine, alkylated N-methylglycine, or precursor of N-methylglycine is administered at a dosage equivalent to 10 mg to 100 g of N-methylglycine.

30. The method of claim 28, wherein the glycine uptake inhibitor is an ester of N-methylglycine having an ester group with 1-20 carbon atoms.

31. The method of claim 28, wherein glycine uptake inhibitor is an alkylated N-methylglycine having an alkyl group with 1-20 carbon atoms.

32. The method of claim 28, wherein the precursor is selected from the group consisting of N,N,N-trimethylglycine and N,N-dimethylglycine.

33. The method of claim 1, wherein the pharmaceutical composition is administered to the patient at least once daily for at least one week.

34. The method of claim 1, further comprising administering to the patient at least one therapeutic selected from the group consisting of antipsychotics, antidepressants, psychostimulants, and Alzheimer's disease therapeutics.

35. A pharmaceutical composition comprising (i) at least one agonist of the glycine site of an NMDA receptor or at least one glycine uptake inhibitor and (ii) at least one therapeutic agent selected from the group consisting of antipsychotics, antidepressants, psychostimulants, and Alzheimer's disease therapeutics, wherein:

the agonist is selected from the group consisting of D-alanine, a salt of D-alanine, an ester of D-alanine, alkylated D-alanine, a precursor of D-alanine, D-serine, a salt of D-serine, an ester of D-serine, alkylated D-serine, a precursor of D-serine, D-cycloserine, a salt of D-cycloserine, an ester of D-cycloserine, a precursor of D-cycloserine, and alkylated D-cycloserine; and

the pharmaceutical composition is substantially free of D-cycloserine when the agonist is D-alanine, a salt of D-alanine, an ester of D-alanine, an alkylated D-alanine, or a precursor of D-alanine; and

when the agonist is D-cycloserine, a salt of D-cycloserine, an ester of D-cycloserine, a precursor of D-cycloserine, or alkylated D-cycloserine, the pharmaceutical composition comprises an amount of the agonist equivalent to 105-500 mg of D-cycloserine.

36. The pharmaceutical composition of claim 35, wherein the glycine uptake inhibitor is selected from the group consisting of N-methylglycine, a salt of N-methylglycine, an ester of N-methylglycine, alkylated N-methylglycine, and a precursor of N-methylglycine.

37. The pharmaceutical composition of claim 36, wherein the therapeutic agent is an antipsychotic selected from the group consisting of typical antipsychotics, atypical antipsychotics, and depot antipsychotics.

38. The pharmaceutical composition of claim 36, wherein the therapeutic agent is selected from the group consisting of Chlorpromazine, Thioridazine, Mesoridazine, Fluphenazine, Perphenazine, Trifluoperazine, Thiothixene, Haloperidol, Loxapine, Molindone, Clozapine, Risperidone, Olanzapine, Quetiapine, Haloperidol decanoate,

Fluphenazine decanoate, Fluphenazine enanthate, Amitriptyline, Amoxapine, Bupropion, Bupropion SR, Clomipramine, Desipramine, Doxepin, Fluoxetine, Fluvoxamine, Imipramine, Maprotiline, Mirtazapine, Nefazodone, Nortriptyline, Paroxetine, Phenelzine, Protriptyline, Sertraline, Tranylcypromine, Trazodone, Trimipramine, Venlafaxine, Venlafaxine XR, Dextroamphetamine, Methamphetamine, Methylphenidate, Pemoline, Donepezil, Tacrine, Acetophenazine, Chlorprothixene, Droperidol, Pimozide, Butaperazine, Carphenazine, Remoxipride, Piperacetazine, Sulpiride, and Ziprasidone.

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(57) Abstract

The invention provides methods for treating neuropsychiatric disorders such as schizophrenia, Alzheimer's Disease, autism, depression, benign forgetfulness, childhood learning disorders, close head injury, and attention deficit disorder. The methods entail administering to a patient diagnosed as having a neuropsychiatric disorder a pharmaceutical composition containing (i) a therapeutically effective amount of D–alanine (or a modified form thereof), provided that the composition is substantially free of D–cycloserine, and/or (ii) D–serine (or a modified form thereof), and/or (iii) 105 to 500 mg of D–cycloserine (or a modified form thereof), and/or (iv) N–methylglycine (or a modified form thereof).

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	RAMAKRISHNA, T. ET AL: "Betaine reverses toxic effects of aluminum: implications in Alzheimer's disease (AD) and AD-like pathology" CURRENT SCIENCE, vol. 75, no. 11, 10 December 1998 (1998-12-10), pages 1153-1156, XP002117971 the whole document ---	1,3,32
X	EP 0 387 867 A (G.D. SEARLE & CO.) 19 September 1990 (1990-09-19) the whole document especially page 6, line 40-50 --- -/--	1-3,6,7, 10-14, 21-26,33

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 112 863 A (HASHIMOTO ET AL) 12 May 1992 (1992-05-12) the whole document	1,2,10, 11,14, 16,17, 20-23, 26-29, 31,33
X	WO 89 05144 A (G.D. SEARLE & CO.) 15 June 1989 (1989-06-15) the whole document	1,3,6,7, 9,21-23, 27,33
X	WO 97 20552 A (ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY) 12 June 1997 (1997-06-12) the whole document	1-3,5,33
X	WO 97 20553 A (JAVITT, D.C.) 12 June 1997 (1997-06-12) the whole document	1-3,5,33
X	EP 0 432 039 A (NIPPON OILS & FATS CO. LTD.) 12 June 1991 (1991-06-12) the whole document	1,2, 10-14, 16-27,33
X	EP 0 696 586 A (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 14 February 1996 (1996-02-14) the whole document especially page 15, line 20-23	1-4,6,7, 16,17,33
X	DE 41 17 629 A (MAX PLANCK GESELLSCHAFT ZUR FÖRDERUNG DER WISSENSCHAFTEN) 3 December 1992 (1992-12-03) the whole document	1,3,5, 16,18,33
X	JAVITT, DANIEL C. ET AL: "Reversal of phencyclidine-induced hyperactivity by glycine and the glycine uptake inhibitor glycyldodecylamide" NEUROPSYCHOPHARMACOLOGY, vol. 17, no. 3, September 1997 (1997-09), pages 202-204, XP002117972 the whole document	1,2,33
X	JAVITT DC ET AL: "Glycyldodecylamide, a phencyclidine behavioral antagonist, blocks cortical glycine uptake: implications for schizophrenia and substance abuse." PSYCHOPHARMACOLOGY (BERL), JAN 1997, 129 (1) P96-8, XP002117973 GERMANY the whole document	1,2,33

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
X	VAN BERCKEL BN ET AL: "Efficacy and tolerance of D-cycloserine in drug-free schizophrenic patients." BIOL PSYCHIATRY, DEC 15 1996, 40 (12), pages 1298-1300, XP002117974 UNITED STATES the whole document	1,2,21, 33
X	GOFF, D.C. ET AL: "Dose-finding trial of D-cycloserine added to neuroleptics for negative symptoms of schizophrenia" THE AMERICAN JOURNAL OF PSYCHIATRY, vol. 152, no. 8, August 1995 (1995-08), pages 1213-1215, XP002117975 the whole document	1,2, 21-23, 33-38
X	GOFF, D.C. ET AL: "D-cycloserine addedto clozapine for patients with schizophrenia" THE AMERICAN JOURNAL OF PSYCHIATRY, vol. 153, no. 12, December 1996 (1996-12), pages 1628-1630, XP002117976 the whole document	1,2, 21-23, 33-38
X	BAXTER, MARK G. ET AL: "Modulation of the NMDA receptor complex by D-cycloserine" CNS DRUG REVIEWS, vol. 1, no. 1, 1995, pages 74-90, XP002117977 the whole document	1-3, 21-23,33
X	SCHUSTER GM ET AL: "D-cycloserine reverses the working memory impairment of hippocampal-lesioned rats in a spatial learning task." EUR J PHARMACOL, NOV 24 1992, 224 (1) P97-8, XP002117978 NETHERLANDS the whole document	1,3, 21-24,33
X	RIEKKINEN, P. SR. ET AL: "The effects of D-cycloserine on cognition in experimental models of Alzheimer's disease." NEUROLOGY, vol. 43, no. 4, 1993, page A292 XP002117979 abstract	1,3, 21-23,33
X	BAXTER MG ET AL: "D-cycloserine, a novel cognitive enhancer, improves spatial memory in aged rats." NEUROBIOL AGING, MAR-APR 1994, 15 (2) P207-13, XP002117980 UNITED STATES the whole document	1,3,6, 21-23,33

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SIRVIO J ET AL: "D-cycloserine, a modulator of the N-methyl-D-aspartate receptor, improves spatial learning in rats treated with muscarinic antagonist." NEUROSCI LETT, NOV 9 1992, 146 (2) P215-8, XP002117981 NETHERLANDS the whole document	1,3,21, 33
X	MATSUOKA N ET AL: "D-cycloserine, a partial agonist at the glycine site coupled to N-methyl-D-aspartate receptors, improves visual recognition memory in rhesus monkeys." THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 278, no. 2, 1996, pages 891-897, XP002117982 UNITED STATES the whole document	1,3,21, 33
X	FISHKIN R.J. ET AL: "D-cycloserine attenuates scopolamine-induced learning and memory" BEHAVIORAL AND NEURAL BIOLOGY 59/2 (150-157), vol. 59, no. 2, 1993, pages 150-157, XP000565972 United States the whole document	1,3,21, 33
X	"D-Cycloserine: Cognition enhancer." DRUGS OF THE FUTURE, vol. 19, no. 11, 1994, pages 988-91, XP002117983 the whole document	1,3,21, 33
X	CHESSELL IP ET AL: "D-cycloserine, a putative cognitive enhancer, facilitates activation of the N-methyl-D-aspartate receptor-ionophore complex in Alzheimer brain." BRAIN RESERCH, NOV 29 1991, vol. 565, no. 2, pages 345-348, XP002117984 NETHERLANDS the whole document	1,3,21, 33
X	FRANCIS P.T ET AL: "A GLYCINE SITE AS THERAPEUTIC TARGET" ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 640, 1991, pages 184-188, XP002117985 the whole document	1,3,21, 33

-/--

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US AN: 95000475, XP002117994 abstract & VAMVAKIDES, A.: "Nootropic activity of glycinergic derivatives in relation to their dualistic effects on cerebral monoamines" BOLL CHIM FARMA, vol. 133, no. 6, 1994, pages 369-373, ---	1,3,21, 33
X	TEMPLE, MEREDITH D. ET AL: "Chronic, post-injury administration of D-cycloserine, an NMDA partial agonist, enhances cognitive performance following experimental brain injury" BRAIN RESEARCH, vol. 741, no. 1,2, 1996, pages 246-251, XP002117986 the whole document ---	1,9, 21-23,33
X	PAPP, MARIUSZ ET AL: "Antidepressant-like effects of 1-aminocyclopropanecarboxylic acid and D-cycloserine in an animal model of depression" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 316, no. 2/3, 1996, pages 145-151, XP002117987 the whole document ---	1,5,21, 33
X	NILSSON, M. ET AL: "Glycine and D-serine decrease MK-801-induced hyperactivity in mice" JOURNAL OF NEURAL TRANSMISSION, vol. 104, no. 11-12, 1997, pages 1195-1205, XP002117988 the whole document ---	1,2,16, 17,33
X	CONTRERAS, P.: "D-serine antagonized phencyclidine- and MK-801-induced stereotyped behaviour and ataxia" NEUROPHARMACOLOGY, vol. 29, no. 3, March 1990 (1990-03), pages 291-293, XP002117989 the whole document --- -/--	1,2,16, 17,33

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAMAKERS, G. M. J. ET AL: "The impaired long-term potentiation in the CA1 field of the hippocampus of cognitive deficient microencephalic rats is restored by D-serine" NEUROSCIENCE , vol. 54, no. 1, 1993, pages 49-60, XP002117990 OXFORD the whole document ---	1,3,4,6, 7,9,16, 33
X	DATABASE WPI Week 8013 Derwent Publications Ltd., London, GB; AN 80-22600C XP002117996 & JP 55 020747 A (SUMITOMO CHEM CO LTD), 14 February 1980 (1980-02-14) abstract ---	1,5,16, 17,33
X	DATABASE WPI Week 9614 Derwent Publications Ltd., London, GB; AN 96-136177 XP002117997 & JP 08 026986 A (YAMANOUCHI PHARM CO LTD) , 30 January 1996 (1996-01-30) abstract ---	1-4,6, 16,17, 19,20,33
X	DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL AN:1996314437, XP002117995 abstract & NISHIKAWA, T. ET AL: "PCP-induced abnormal behaviour and c-fos gene expression in the brain as indices for neuroleptic-resistant symptoms of schizophrenia" FOLIA PHARMACOLOGICA JAPONICA, vol. 108, no. suppl. 1, 1996, pages 53P-58P, ---	1,2,10, 16,17,33
X	TANII, Y. ET AL: "Effects of allosteric agonists for NMDA receptor and their derivatives on PCP-induced abnormal behaviours in rat" THE JAPANESE JOURNAL OF PSYCHIATRY AND NEUROLOGY, vol. 44, no. 4, December 1990 (1990-12), page 790 XP002117991 the whole document --- -/--	1,2,10, 16,17, 19,33

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/08056

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TANII, Y. ET AL: "Stereoselective antagonism by enantiomers of alanine and serine of phencyclidine-induced hyperactivity, stereotypy and ataxia in the rat" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 269, no. 3, 1994, pages 1040-1048, XP002117992 the whole document ---	1,2,10, 11,16, 17,33
X	RIMLAND, B.: "Dimethylglycine (DMG), a nontoxic metabolite and autism" AUTISM RESEARCH REVIEW INTERNATIONAL, vol. 4, no. 2, 1990, page 3 XP002117993 the whole document -----	1,4,28, 29,32-36

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

ernational application No.

PCT/US 99/ 08056

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-34
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 1-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/08056

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 387867 A	19-09-1990	US 5061721 A	29-10-1991
		AT 88890 T	15-05-1993
		AU 624917 B	25-06-1992
		AU 5073490 A	20-09-1990
		CA 2010635 A	15-09-1990
		DK 387867 T	01-06-1993
		ES 2055197 T	16-08-1994
		GR 3008225 T	30-09-1993
		IE 64130 B	12-07-1995
		IL 93562 A	31-01-1996
		JP 3148221 A	25-06-1991
		PT 93424 A,B	07-11-1991
		US 5260324 A	09-11-1993
US 5112863 A	12-05-1992	JP 3236315 A	22-10-1991
		EP 0432039 A	12-06-1991
WO 8905144 A	15-06-1989	US 4904681 A	27-02-1990
		AT 68698 T	15-11-1991
		AU 1083992 A	07-05-1992
		AU 2631988 A	01-06-1989
		AU 2813089 A	05-07-1989
		AU 7746794 A	05-01-1995
		CA 1328617 A	19-04-1994
		DE 3865817 D	28-11-1991
		DK 669088 A	02-06-1989
		EP 0319824 A	14-06-1989
		EP 0421997 A	17-04-1991
		ES 2040314 T	01-04-1995
		GR 3003571 T	16-03-1993
		IE 61825 B	30-11-1994
		JP 5201859 A	10-08-1993
		JP 1193220 A	03-08-1989
		JP 1893241 C	26-12-1994
		JP 6021065 B	23-03-1994
		KR 134198 B	21-04-1998
		PH 26467 A	27-07-1992
		PT 89109 A,B	29-12-1989
		US 5087633 A	11-02-1992
		US 5468763 A	21-11-1995
WO 9720552 A	12-06-1997	CA 2239624 A	12-06-1997
		EP 0871440 A	21-10-1998
		WO 9720553 A	12-06-1997
		US 5837730 A	17-11-1998
		US 5854286 A	29-12-1998
WO 9720553 A	12-06-1997	CA 2239624 A	12-06-1997
		EP 0871440 A	21-10-1998
		WO 9720552 A	12-06-1997
		US 5837730 A	17-11-1998
		US 5854286 A	29-12-1998
EP 432039 A	12-06-1991	JP 3236315 A	22-10-1991
		US 5112863 A	12-05-1991
EP 696586 A	14-02-1996	AU 681655 B	04-09-1997
		AU 6582494 A	21-11-1994

Form PCT/ISA/210 (patent family annex) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/08056

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 696586 A		US 5834460 A	10-11-1998
		CA 2160459 A	10-11-1994
		CN 1121713 A	01-05-1996
		HU 75032 A	28-03-1997
		WO 9425450 A	10-11-1994
DE 4117629 A	03-12-1992	NONE	
JP 55020747 A	14-02-1980	NONE	
JP 8026986 A	30-01-1996	NONE	